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Treatment of Cerebellar Ataxia in the Context of Systemic Diseases

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Abstract

Purpose of review The purpose of this review is to assess the evidence behind treatment regimens for cerebellar ataxias occurring in the context of systemic disease. We will address systemic conditions which are associated with specific involvement of the cerebellum (rather than widespread nervous system involvement) and those conditions for which some degree of evidence of treatment response exists.

Recent findings We have divided systemic disorders affecting the cerebellum into systemic immunological disorders, endocrine and metabolic disorders and paraneoplastic. Recent studies have increased understanding of the range of cerebellar disorders associated with a systemic immunological condition. The identification of newer pathogenic antibodies has improved diagnosis in conditions which would have previously been labelled as idiopathic. However, their rarity and phenotypic variability makes defining optimal immunomodulatory treatment regimens challenging. There is some evidence for beneficial effects of immunomodulation, particularly in anti-GAD ataxia and Hashimoto's encephalopathy, although, at this time, specific treatment regimens cannot be defined. Immune-mediated paraneoplastic cerebellar disorders show response to therapy dependent, to some extent, on the underlying pathogenic antibody. Much is still to be understood concerning treatment regimens for the ataxic manifestations of metabolic disorders, notably alcohol-induced cerebellar injury, which are common and which are associated with significant disability.

Summary Despite their rarity, cerebellar ataxias occurring in the context of systemic disease cause significant morbidity and better therapies are required to improve outcomes associated with these conditions.

Introduction

Dysfunction of the cerebellum can occur either as a result of localised injury or in the context of a number of systemic diseases. Systemic disorders often affect the central nervous system diffusely, but, in a number of situations, may specifically cause cerebellar dysfunction. Within this review, cerebellar ataxia in the context of systemic diseases will be considered. Broadly, systemic

disorders affecting the cerebellum may be divided into systemic immunological disorders, endocrine and metabolic disorders and paraneoplastic. While some of the conditions discussed have no specific treatment, there are emerging studies suggesting specific conditions may respond to particular treatments.

Ataxia and systemic immunological disorders

Anti-GAD ataxia

Non-paraneoplastic autoimmune cerebellar ataxia was first defined some 20 years ago with the identification of antibodies, in both serum and CSF, directed against the enzyme glutamic acid decarboxylase (GAD) [1]. Since the earliest reports, a strong association between anti-GAD and systemic autoimmune conditions has been confirmed, including type 1 diabetes, pernicious anaemia, vitiligo and thyroiditis [2]. Yet, the cerebellum should in itself be considered a primary target organ for autoimmunity, as evidenced by the high proportion of HLA type DQ2 and the demonstration of cerebellar antibodies in some 60% of patients with otherwise idiopathic ataxia [3]. The cerebellum therefore, alongside the hippocampus, appears particularly vulnerable to immune-mediated pathology—mechanistic evidence is strongest for the GAD65 isoform, probably via (reversible) interference in GABA exocytosis (reviewed in [4•]) but also resulting in (irreversible) Purkinje cell loss [5]. Anti-GAD disease may present clinically with either sub-acute or chronic ataxia, potentially accompanied by features of overlapping neurological conditions also attributed to anti-GAD, including stiff-person syndrome [6]. Therapeutic approaches may therefore simultaneously need to target symptomatic relief of muscle rigidity with GABAergic agonists such as diazepam [7]. A meaningful impact on ataxic symptoms is less reliably achieved, although baclofen was reportedly of benefit for periodic alternating nystagmus [8]. Outside the context of anti-GAD disease, aminopyridines may relieve downbeat nystagmus [9] while acetyl-DL-leucine shows promise among unselected ataxia cases [10] but awaits placebo-controlled confirmation [11].

With the expectation that most patients with anti-GAD cerebellar ataxia will accumulate significant disability [12], consideration is often given to immunosuppression despite the lack of evidence from placebo-controlled trials [13]. Overall, the reported results of treatment are mixed, with the largest case series reporting 'robust' responses in a higher proportion of 55 non-paraneoplastic cerebellar ataxia patients compared with 63 paraneoplastic cases [14••]. Over half of the non-paraneoplastic cases in this series responded to immunotherapy, typically including long-term maintenance. Long-term follow-up data has also been reported for a further 25 ataxia patients with GAD65 antibodies in whom 35% experienced an improvement of at least 1 point on the modified Rankin Scale [15•]. Sub-acute presentations carried a more favourable prognosis than chronic ataxia. Varying induction regimes combining steroids,

intravenous immunoglobulins (IVIg) and plasma exchange (PEX) have been utilised, typically relying on clinical status to assess response, although neurophysiological outcome markers may also inform [16]. While decreases in serum, anti-GAD levels have often tracked effective therapy, for example with rituximab [17], intrathecal levels may be more reflective of treatment response [18]. Further uncertainty surrounds cases of cerebellar ataxia with low (< 100 U/ml) serum titres of anti-GAD, in whom responses to immunotherapy are sparsely described [19, 20]. Antibodies against the GAD67 epitope may potentially also be pathogenic [21]. Evidence-based recommendations for maintenance therapy are not currently possible but previous choices have included azathioprine and mycophenolate (discussed in [22]).

Gluten ataxia

Anti-GAD antibodies have also been detected in 40% of a well-defined cerebellar ataxia cohort curated in Sheffield, UK [23]. These patients, however, had an existing diagnosis of *gluten ataxia* suggesting therefore an overlapping spectrum of cerebellar autoimmunity. This neurological syndrome is infrequently the presenting clinical feature of coeliac disease, antibodies to gliadin and/or transglutaminase are accordingly detectable in between 10 and 50% of sporadic ataxia patients, depending on the background population [24]. Coeliac disease is also held responsible for cases of peripheral neuropathy [25] and other diverse neurological manifestations, yet, not all gluten ataxia patients have biopsy evidence of enteropathy and few have gastrointestinal symptoms; conversely 37% of newly diagnosed coeliac patients exhibit neurological signs in one report [26].

While randomised trial data concerning treatment of gluten ataxia is lacking, the broader necessity for systemic control of coeliac disease applies equally to this subgroup [27]. Strict adherence to a gluten-free diet is therefore recommended. A single pragmatically designed study investigated the impact on gluten ataxia on 26 patients who adhered to the diet compared at baseline to 14 patients who declined the intervention [28]. Diet-compliant patients, regardless of whether enteropathy was initially detectable, showed significant improvement across a range of ataxia clinical measures. Further mechanistic evidence in support of gluten avoidance is provided by a recent MR spectroscopy study in which a normalisation of NAA/Cr ratio in the cerebellar vermis resulted from successful diet adherence (as indexed by elimination of detectable anti-gliadin antibodies); the effect was diminished by partial adherence [29]. Symptomatic improvement is typically delayed by approximately 1 year and ataxia may only stabilise in advanced cases with established cerebellar atrophy. Whether incremental benefit is likely with simultaneous immunosuppression remains to be determined; isolated reports describe clinical improvement with IVIg [30], even among cases refractory to gluten-free diet [31].

Ataxia and systemic endocrine/metabolic disorders

Alcohol-induced cerebellar disease

Chronic excessive alcohol ingestion is a common cause of cerebellar degeneration. Clinically, patients present with ataxia predominantly affecting legs and gait, and typically occurs in association with features of malnutrition. Some

patients may present acutely with Wernicke encephalopathy (WE), which has the added features of delirium, cognitive impairment and oculomotor deficits. The association of WE and thiamine (vitamin B₁) deficiency is well-recognised; however, it remains unclear to what extent chronic alcohol-induced cerebellar damage is caused by the effects of thiamine deficiency or directly attributable to the toxic effects of alcohol on the brain [32]. Abstinence from alcohol and thiamine supplementation remains the mainstay of treatment.

Abstinence from alcohol was also shown to result in clinically relevant improvement in chronic alcoholic cerebellar degeneration, as assessed by measures of postural instability over 18 months [33]. A further study (over 2 years) confirmed that abstinence can improve postural stability and may be linked to changes in fourth ventricular size [34]. Perhaps not surprisingly, long-term abstinence (> 18 months) is associated with better recovery of gait and balance problems above and beyond short-term abstinence (6–15 weeks) [35].

Regarding thiamine replacement, its role in WE is established. However, a recent Cochrane review only found two randomised trials and no firm conclusion regarding the dose, route of administration and minimum duration for treatment or prophylaxis against WE could be made [36••]. In practice, due to unreliable absorption of thiamine in malnourished patients, it is recommended that thiamine is administered intravenously in acute WE, although only class IV evidence exists to back up this guidance [37]. Whether thiamine replacement is of benefit in chronic alcoholic ataxia is unknown, but typically, patients are prescribed with vitamin supplementation. The fact that WE can occur in the setting of poor nutrition unrelated to alcoholism suggests that thiamine replacement is likely to be of benefit in patients who have become abstinent, although evidence is lacking. There is no evidence that thiamine replacement is effective in improving ataxia in those with established chronic alcoholic cerebellar degeneration.

Thyroid disease and ataxia

Ataxia has been reported in hypothyroidism [38]. However, whether a lack of thyroid hormone genuinely causes cerebellar dysfunction is not clear. Hypothyroidism is common and the rarity of ataxia in the condition may suggest a lack of causality and possibly coincidence of separate diseases [39]. Gait problems in hypothyroidism may often be attributed to the typical changes in muscle contractility that occurs. Treatment with thyroxine is routine and typically improves systemic features of the disease.

Hashimoto's encephalopathy (HE) is a neurological condition associated with elevated anti-thyroid antibodies (anti-thyroglobulin or anti-thyroid peroxidase (TPO)), often occurring in euthyroid individuals [40]. Since anti-TPO antibodies can occur in the healthy general population, the diagnosis may be challenging. Antibodies against NH₂-terminal of α -enolase (NAE) have been reported as a useful serum biomarker of HE [41]. Reports have suggested that HE may rarely present as an isolated ataxic syndrome. A case series of 13 adult patients (of whom eight had anti-NAE antibodies) with a predominantly ataxic form of HE reported that truncal ataxia is common and nystagmus is uncommon, and eight out of 13 had a syndrome mimicking spinocerebellar degeneration with insidious onset [42]. One of

the cardinal features of HE is its responsiveness to immunotherapy (hence, the alternative nomenclature of steroid-responsive encephalopathy associated with autoimmune thyroiditis [SREAT]). A recent study of 13 patients with anti-NAE HE reported full or good recovery in 11 patients treated with methylprednisolone with or without prednisolone tail (one patient also received plasma exchange) [43]. In the case series of ataxic HE mentioned above, all patients responded to steroid treatment and/or IVIg [42]. Response appeared better in those with anti-NAE antibodies although the study size was small. Despite the usually good response to steroid therapy, relapse after steroid withdrawal may occur and optimal maintenance therapy is not clear. There is no trial evidence but reports have described use of azathioprine, mycophenolate mofetil, methotrexate, cyclophosphamide, rituximab, maintenance IVIg and plasma exchange [44–46].

Paraneoplastic ataxic manifestations

Paraneoplastic syndromes within the central nervous system (CNS) refer to non-metastatic involvement of the brain and/or spinal cord, most likely occurring as a result of an immune reaction to cancer cells generating antibodies which cross-react with CNS antigens [47]. They occur rarely, but of the described CNS paraneoplastic syndromes, paraneoplastic cerebellar degeneration (PCD) is the commonest.

Paraneoplastic cerebellar degeneration

Fifty to 60% of patients with paraneoplastic cerebellar degeneration (PCD) have identifiable antibodies in serum and/or CSF, of which anti-Yo (alternatively referred to as anti-Purkinje cell cytoplasmic antibody-1; PCA-1) is the commonest, representing approximately 50% of antibody-positive PCD [48]. PCD typically presents with sub-acute onset of ataxia which, often rapidly, progresses to pan-cerebellar failure. Often, cerebellar features plateau after a period of time. PCD may occur as an isolated cerebellar syndrome usually associated with breast or ovarian cancer and anti-Yo antibodies, or with Hodgkin's lymphoma and Tr/DNER antibodies [49]. Alternatively, PCD presents in association with other neurological features such as encephalomyelitis (small cell lung cancer and anti-Hu antibodies) [50] or eye movement abnormalities (typically, opsoclonus with breast or ovarian cancer and anti-Ri antibodies) [51]. The repertoire of antibodies associated with PCD is increasing, now including antibodies against the Purkinje cell protein carbonic anhydrase-related protein VIII (CARP) [52] and protein kinase C γ (PKC γ) [53]. It seems likely that further antibodies will be discovered identifying a cause in antibody-negative PCD cases.

In general, PCD responds poorly to treatment. The rarity of the condition, coupled to the multiple antibodies that may cause the phenotype, has meant that randomised controlled trials of PCD therapies are lacking. In addition, the rather rapid disease onset followed by plateau renders determination of treatment efficacy challenging.

Treatment or removal of the underlying tumour, if possible, is important, although even if successful, often, the symptoms of PCD do not

improve and the majority of patients with PCD will remain severely disabled [50, 54]. Prognosis is poor and median survival in a study of 34 anti-Yo PCD cases was 22 months [54]. Studies have suggested that prognosis may be slightly better in PCD associated with antibodies other than anti-Yo [55]. Indeed, improvement in PCD associated with anti-Tr antibodies and Hodgkin's lymphoma has been reported following treatment of the cancer [56].

Studies have assessed the utility of additional immunotherapy in PCD. The outcomes are generally disappointing although some small case series have reported benefit (class IV evidence). Immunotherapies such as corticosteroids, IVIg and PEx have been most studied. PEx has been reported to cause improvement in some cases, although the majority of reported cases do not appear to improve [57]. Similarly, IVIg has been reported to be effective in single cases, although a study of 22 patients with anti-neuronal antibody-associated paraneoplastic neurological syndromes (including 4 with PCD) did not reveal any effect on disability using IVIg (median 5.8 cycles) [58–62]. The most commonly reported alternative immunosuppressant is cyclophosphamide, but, again, evidence is limited only to single cases [63, 64]. Aggressive combination immunosuppressive regimes have been reported [65]. A follow-up study of 17 patients with anti-Yo and anti-Hu paraneoplastic encephalomyelitis, sensory neuropathy or PCD receiving cycles of IVIg, cyclophosphamide and methyl prednisolone reported clinical stabilisation (evaluated by the modified Rankin scale) in those patients who were not severely disabled at time of treatment onset, but no effect in severely disabled PCD patients [66]. It remains unclear whether early administration of immunosuppression in PCD improves prognosis.

Newer therapies including tacrolimus and rituximab have been studied in case reports or small case series in PCD. Rituximab has been reported to induce partial remission in individual cases [67–69]. Tacrolimus, a potent T cell inhibitor, has been studied in a series of patients with paraneoplastic neurological disease (including PCD) [70]. Although, the trial was not designed to quantify neurological outcome, there were anecdotal reports in some patients of improvement in function. More studies are required to determine the influence of immunosuppressive regimes on PCD.

Conclusion

There is some evidence concerning treatment regimens for cerebellar ataxias occurring in the context of systemic disease. Cerebellar ataxia occurring in the context of a systemic immunological disorder is often amenable to a range of immunomodulatory therapies, although the rarity of these disorders and the phenotypic variability makes defining optimal treatment regimens challenging. The commoner ataxic manifestations of metabolic disorders, notably alcohol-induced cerebellar injury, have been the subject of several studies, although there is a paucity of evidence concerning optimal treatments for chronic alcoholic cerebellar degeneration. Despite their rarity, cerebellar ataxias occurring in the context of systemic disease cause significant morbidity and better therapies are required to improve outcomes associated with these conditions.

Compliance with Ethical Standards

Conflict of Interest

Malcolm Proudfoot declares no potential conflicts of interest. Alastair Wilkins is a section editor for *Current Treatment Options in Neurology*.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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